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NEUROVASCULAR NEWS

The Brain Aneurysm Institute

Multidisciplinary Care of Patients with Hemorrhagic and Ischemic Stroke



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Arteriovenous Malformations

Introduction

Arteriovenous malformations (AVMs) of the brain are thought to be a congenital abnormal development of the cerebral vasculature with a tangle of vessels that shunts blood from the arterial to the venous system. AVMs are defined histopathologically as abnormal vessels with elements of arteries and veins with intervening neural tissue. The functionality of the intervening neural tissue is variable which is why lesions can be treated in many instances safely. Patients can present with seizures, hemorrhage or as incidental lesions. The decision-making process as to whether or not to treat an AVM once the diagnosis is made is influenced by many factors. Lesions can be managed conservatively, treated with surgical excision, endovascular embolization or focused radiation (radiosurgery) or combinations of these management strategies. In this edition of the neurovascular news, we will detail the natural history of these lesions as well as the various risks and benefits involved with the treatment options.

Natural History of Arteriovenous Malformation

Christopher S. Ogilvy, MD

Intracranial arteriovenous malformations (AVM) are most often diagnosed in young and middle-aged adults. While hemorrhage remains the most common presentation for patients with an AVM, the development of high quality non-invasive vascular imaging has increased the detection of unruptured AVMs. The diagnosis of an asymptomatic but potentially life-threatening condition in a young person makes understanding the natural history of these lesions critical for therapeutic decision making.

The overall annual rate of hemorrhage for AVMs is estimated at 4% per year.¹³ This risk is significantly influenced by the presence of a previous hemorrhage.⁷ Risk of rupture from an unruptured AVM is reported at just over 2% per year,^{3,11} while the risk of re-bleeding within the first year increases to 7%,⁴ with a gradual return to the baseline rate over subsequent years. Several morphological and angio-architectural features have been reported as risk factors for hemorrhage. Among these, deep brain location, exclusive deep venous drainage, feeding vessel aneurysm, increasing age, and restriction of venous drainage have been the most consistently associated with hemorrhage risk.^{6,9,15} When compared to intracerebral hemorrhage (ICH) patients from causes other than AVM, patients suffering an AVM related ICH have more favorable outcomes with lower odds of death and higher odds of discharge home. This finding

remained significant after adjustment for demographics, medical comorbidities, and surrogates of ICH severity.¹²

Lifetime hemorrhage risk can be estimated with the following formula: Risk of hemorrhage $\approx 105 - \text{Age}$ in years. This assumes a 3% per year rupture rate.

Seizures unrelated to hemorrhage is the second most common presentation, affecting up to 30% of patients with a brain AVM.^{2,8} The risk of de novo epilepsy related to an unoperated brain AVM has been reported at 18% over 20 years of follow-up. Risk factors included AVM hemorrhage and AVM location in the temporal lobe. No patient presenting with an incidentally discovered AVM developed epilepsy during the follow-up period.⁵ Headache represents another presenting symptom prompting cranial imaging and leading to the diagnosis of a brain AVM. However, the association between AVMs and headache unrelated to hemorrhage remains unproven.

Spontaneous and complete regression of brain AVMs has been reported but is a rare occurrence with only 62 cases identified in the English literature as of 2002.¹⁴ The vast majority of these AVMs had a single draining vein and were associated with hemorrhage.^{1,14} It is hypothesized that occlusion of the single draining vein leads to outflow obstruction and thrombosis. Hemorrhagic presentation and a small nidus may also predispose to spontaneous obliteration.¹

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Embolization of Brain Arteriovenous Malformations

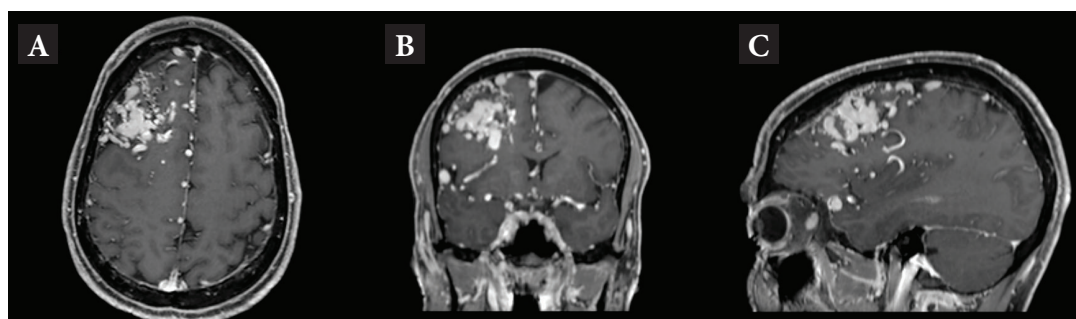
Georgios A. Maragkos, MD, Christopher S. Ogilvy, MD, Ajith J. Thomas, MD

Treatment of brain arteriovenous malformations (AVM) can be achieved through surgery, radiation, or embolization, either as a single modality or in combination.¹⁻³ In our center, embolization is mainly used to reduce the size of large AVMs to enhance the safety and decrease length of surgery. Over the last ten years, the Onyx® liquid embolic system (Ev3, Irvine, CA) has become the most commonly used embolic agent. Prior to this, the fast polymerizing liquid adhesive n-butyl cyanoacrylate (n-BCA) was used for

this purpose. Onyx is less adhesive and polymerizes slowly, which seems advantageous over n-BCA.^{4,5}

Indications for Treatment

AVM treatment strategy and indications for embolization are assessed from magnetic resonance imaging (MRI) and angiography at a multidisciplinary team conference, which includes three neurosurgeons who have experience in radiosurgery, embolization and operative resection.



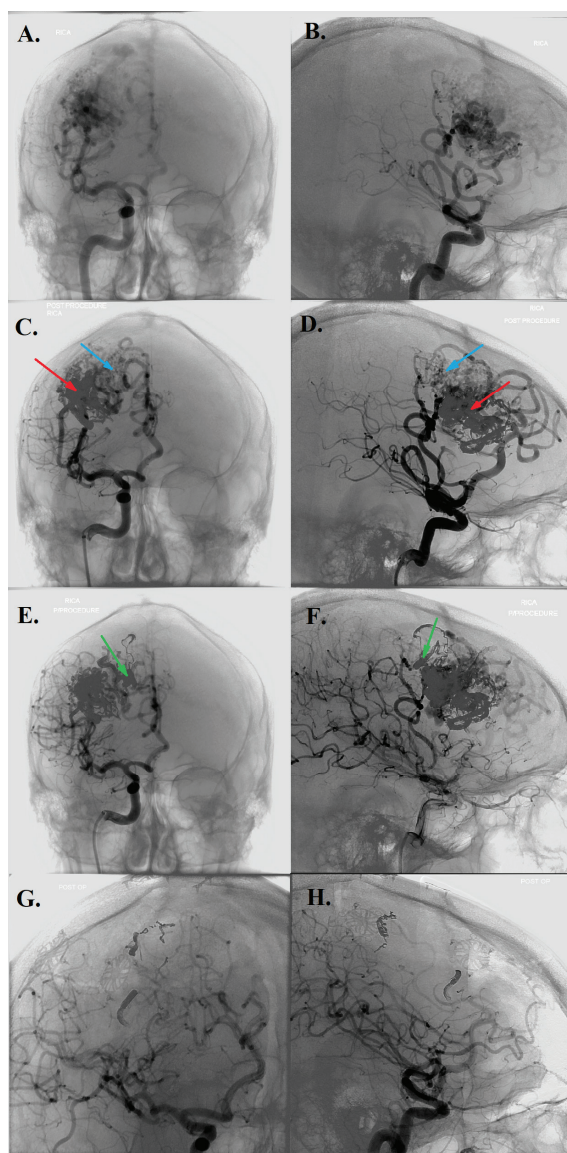
▲ **Figure 1:** Preoperative axial (A), coronal (B) and sagittal (C) T1 post-gadolinium MRI reveals a cluster of serpiginous vessels in the right frontal region. The lesion measures 6.2 x 3.7 x 4.6 cm and is consistent with an arteriovenous malformation.

In general, lesions larger than 3 cm are embolized to achieve size reduction, before they are surgically resected. Smaller AVMs are also embolized, in situations where deep pedicles would have to be accessed late in surgery. We rarely attempt to embolize AVMs with a curative intent. This could lead to unnecessarily aggressive embolization, with potentially higher complication rates. After every embolization session, results are discussed in a joint meeting and additional treatment is planned with either additional embolization or surgery with curative intent. We have generally avoided embolization prior to radiosurgery unless the AVM had hemorrhaged previously.⁶

Technique

Onyx is a liquid embolic agent and is supplied in ready-to-use vials. Each vial contains ethylene-vinyl alcohol copolymer, dimethyl sulfoxide (DMSO), and tantalum. Ethylene-vinyl alcohol copolymer is formed of 48 mol/L ethylene and 52 mol/L vinyl alcohol. The polymer is dissolved in DMSO and is prepared in 2 different concentrations: 6.0% and 8.0%. Micronized tantalum powder (35% wt/vol) is added for radiopacity. The vials are kept on a shaker (Vortex-Genie, Scientific Industries, Bohemia, NY) for at least 20 minutes to ensure proper mixing of the tantalum powder. The lower the concentration of the copolymer, the less viscous the agent and the more distal penetration can be achieved. Viscosity of Onyx at 6.0% and 8.0% concentration is manufactured as Onyx 18 and Onyx 34. Generally, Onyx 18 is used for embolization of the nidus, with Onyx 34 being used for embolization of large arteriovenous shunts in the AVM. Recently, we have migrated to a strategy of just using Onyx 18, with better penetration both into the nidus and feeders.

All embolizations were performed with the patient under general anesthesia on a biplane angiographic unit (Philips Medical Systems, Best, the Netherlands). Systolic blood pressure during the procedure was controlled between 90 and 140 mmHg. Catheterization was performed with a transfemoral approach by using standard coaxial techniques. A DMSO-compatible microcatheter (Apollo Onyx Delivery Microcatheter, Ev3, Irvine, CA) was navigated to the nidus of the AVM with the aid of an 0.008-inch guidewire (Mirage TM Hydrophilic Guidewire, Ev3, Irvine, CA). Once the microcatheter tip was in the desired position, the injection of Onyx was carried out slowly under fluoroscopy.



▲ **Figure 2:** Sequential embolization and open resection of AVM in a 51-year-old man. Anteroposterior (A) and lateral (B) preoperative angiogram images demonstrate a Spetzler-Martin 4 right frontal AVM, supplied by distal hyperplastic branches of the ACA and MCA. There is a rapidly transmitting shunt with mostly superficial venous drainage through the superior sagittal sinus and some deep venous drainage through the straight sinus. The AVM was sequentially embolized using Onyx material. Anteroposterior (C) and lateral (D) angiogram demonstrating the first attempt at embolization (red arrows), along with the residual 50% of the lesion (blue arrows), still filling with contrast. The AVM was re-embolized (E and F, green arrows), to reduce the residual filling. Afterwards, the lesion was resected in an open fashion, as a curative measure. Postoperative angiogram (G and H) demonstrates no residual lesion.

Single injections of Onyx were carried out for up to 30 minutes. Long injection times are possible because of the minimally adhesive nature of Onyx. During injections, we were able to pause, obtain an angiogram to assess nidus occlusion and the status of draining veins, and then continue with the injection. When any reflux of Onyx into the feeding pedicle or venous migration is noted, the injection was stopped for 2-3 minutes to allow for solidification, and then injection was continued. The Onyx then fills a different portion of the nidus, with no further reflux or filling of the vein. When reflux exceeded about 1.5-2 cm of the catheter tip, the catheter was withdrawn with the detachable tip of the Apollo microcatheter sometimes being left in the Onyx cast. Care is taken not to occlude the draining veins at the end of the procedure. In areas of eloquent cortex, provocative testing was performed. Onyx may reflux via the nidus into a remote feeder of the AVM. When this reflux is appreciated on fluoroscopy, injection is immediately stopped. After waiting for 2-3 minutes, other portions of the AVM can be embolized.

Complications of embolization can occur in about 5-10% of procedures with the major complication being neurologic deficits.³ Rarely, mortality of patients, has been reported. The risk of procedures the microcatheter

remaining glued inside the AVM has generally been obviated with the use of Apollo detachable microcatheters.

Our initial experience with use of Onyx for embolization of brain AVMs has been encouraging, with an average size reduction of 70-80% and significant reduction in operative times and blood loss.

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Surgical Treatment of Intracranial Arteriovenous Malformations (AVMs)

Christopher S. Ogilvy, MD, Santiago Gomez-Paz, MD

In order to proceed with a surgical intervention on these complex lesions, several factors must be assessed. Size, location and clinical presentation with a bleeding episode are important considerations to account for in the decision-making process.¹ Patients that present with a hemorrhagic episode can have fatal consequences and the re-hemorrhage risk is fairly high in the first couple of months after such bleeding episode.² This makes the assessment of risks on performing an intervention of an AVM a crucial component to counter act effectively the early period of increased bleeding risk and subsequent cumulative risk of hemorrhage that patients might have.

Age and general health of the patient factor heavily in selecting the appropriate therapy. Older patients with shorter life expectancy may not merit treatment when the lifetime risk of hemorrhage is balanced against the risk of undergoing procedure (see discussion of natural history). If the lesion involves critical brain tissue such as the motor strip or speech areas, the chance for deficit after resection can be high.³ However, given the concept

that AVMs develop as the brain develops, what should be a 'critical' or 'eloquent' area of the cortex can often be shifted due to abnormal tissue surrounding the immediate malformation. This intrinsic nature of the AVM's also help when performing a microsurgical intervention, since it serves as a delineation between normal brain tissue and the vascular malformation.

Since AVM's do not have anatomic constraints and can appear in any part of the brain (figure 1), functional MRI scans have proven helpful in evaluating these lesions and their anatomic surroundings.⁴ For a functional MRI, the patient is instructed

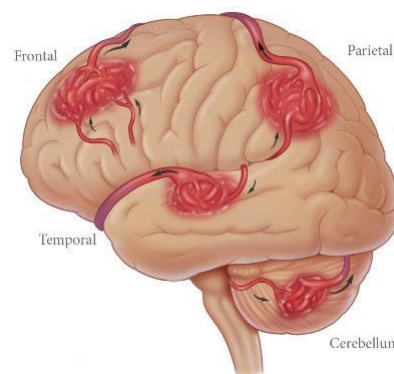
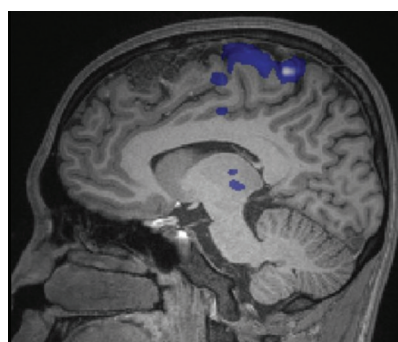
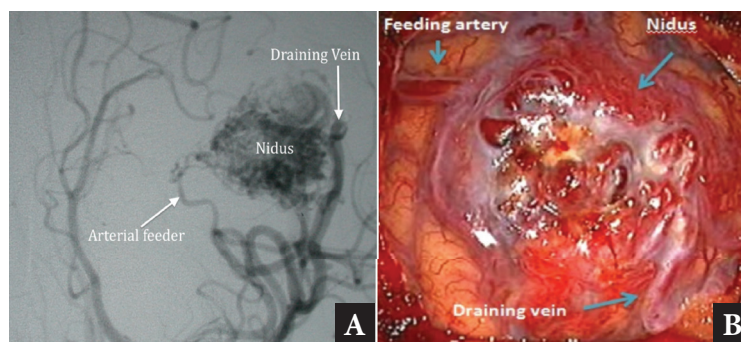


Figure 1: Example of AVM's in various locations.



◀ **Figure 2:** Patient with a left sided frontal lobe AVM undergoing a functional MRI, instructed to move his right leg. The blue area is the area of activation with leg movement.

▶ **Figure 3:** Anatomic components of an AVM
A: Angiogram
B: Microsurgical field



to perform a task during the scan, and then the scan is performed (figure 2). The changes in blood flow associated with the function elicited are detectable on the MRI in normal tissue, hence the location of the function can be detailed. Depending on the proximity of these changes relative to the AVM, risk of resection is assessed. These properties are crucial to evaluate when performing surgery in AVM's located in such risky areas. Another tool frequently used to assess surgical risks of an AVM is the Spetzler scale, which can give the surgeon an approximate risk by considering anatomical components of the malformation, such as feeder vessels, outflow and also functional aspects of the surrounding tissue.⁵

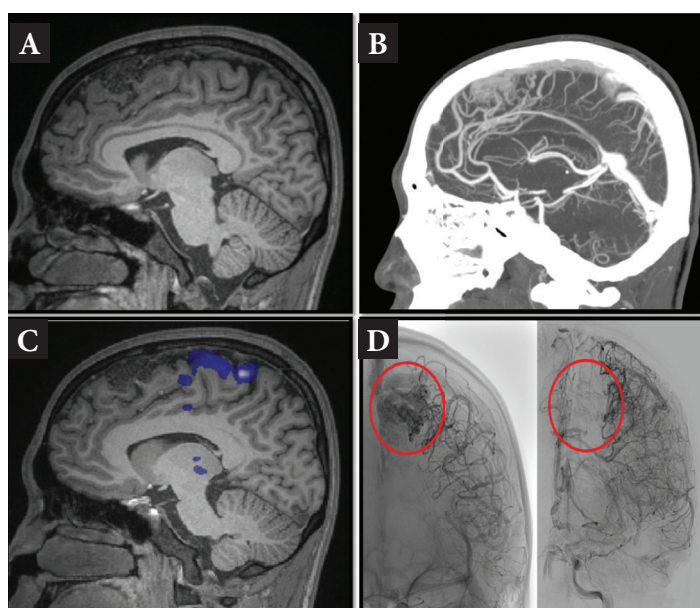
If a patient presents with hemorrhage associated with the AVM, surgical resection of the hematoma can be a life-saving measure. If the hematoma is smaller and the patient has minimal or no neurologic deficit, surgical resection can be deferred several weeks.⁶ This allows the blood to liquify and provides the surgeon with a plane of dissection between the normal brain tissue and the malformation. Endovascular embolization is used when it is felt safe prior to surgical resection.⁷ In this fashion, blood flow is reduced through the AVM prior to surgery.

Surgical excision involves a skin incision and bone removal (replaced after lesion is excised). Once these steps are completed, the AVM is exposed by opening the dura mater. Stereotactic guidance is provided by an MRI scan done the morning of the surgery. The lesion is excised by identifying the 'feeding arteries' which supply arterial blood to the malformation (figure 3). These are carefully dissected free under the microscope and coagulated or clipped. By working in a circumferential fashion around the lesion, all arteries entering the lesion can be excluded. The final steps to excision involve coagulation and transection of the draining vein. Once this is complete, the AVM can be totally removed.

Once the AVM is removed and the craniotomy is closed, an angiogram is obtained to confirm complete resection of the lesion (figure 4, panel D). The patient is then awakened and observed in an ICU overnight for blood pressure monitoring and control. Most patients are typically discharged 2 days after surgery.

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▲ **Figure 4:** 21-year-old male with a left frontal AVM

A: MRI showing lesion in frontal lobe. B: CTA scan characterizing the lesion. C: Functional MRI. D: Pre and post-surgical angiogram comparison.

Radiosurgery for Arteriovenous Malformations

Justin M. Moore, MD, PhD, Luis C. Ascanio, MD

Stereotactic radiosurgery (SRS) has been used to treat arteriovenous malformations (AVMs) for over four decades.^{1,2,4,6,10,11} Since the initial use of Gamma Knife (GK) to treat an AVM in Stockholm in 1970, technological advancements in imaging and computerized AVM targeting have greatly improved radiosurgery, targeting, and dose planning. Proton Beam uses accelerated particles to deliver radiation to a small target.^{1,4} Linear accelerator (LINAC), was first used to treat an AVM in 1983, and most recently the CyberKnife, a frameless system has been developed.⁴ By 2011, over 60,000 patients worldwide had undergone radiosurgery for AVMs. The cure rates are similar among radiosurgical platforms, with rates of 72%, 60%, and 81% achieved with GK, LINAC and CK reported respectively.^{4,10,11} Thus, each of the radiosurgical platforms delivers effective outcomes and low complication rates.

The success of radiosurgery for curing AVM depends upon some of the features of the AVM including the size of the AVM, its location, and the patient age.^{8,10} These factors have been combined to produce a grading system called the radiosurgery-based AVM score (RBAS) to predict the likelihood of an excellent outcome.⁶

How Does it Work?

The targeted radiation produces an injury response to the vessels involved with the AVM. The injured wall of vessel proliferates which ultimately leads to vessel occlusion and eventually destruction of the AVM^{1,2,4,11} (Figure 1). While approximately 80% of AVM are obliterated with radiosurgery, this takes approximately 3 years. During this time there is a small chance the AVM could rupture, approximately 2% per year.^{3,4,10}

Who would be a candidate for Radiosurgery?

The ideal candidate for SRS treatment would be a patient with an AVM that is less than 3.5cm in diameter, as AVM have higher cure rates, particularly if either symptomatic or previously ruptured, and located in deep regions.⁵

Surgical outcomes

Generally, post-SRS obliteration rates fall in the range of 70% to 80%, with higher rates for smaller sized AVMs. AVMs typically do not achieve complete obliteration until 1 to 3 years after SRS treatment, and those that remain patent at 3 to 5 years are considered for retreatment. SRS has also been found to reduce AVM-associated seizures, particularly in those patients whose AVM are obliterated.^{4,10,11}

With ruptured AVMs, large studies have suggested cumulative obliteration rate of 76% with an annual risk of hemorrhage of 2.0%, until the AVM is obliterated. This represents an improvement over natural history estimates of hemorrhage risk in ruptured AVMs and speaks to benefit of SRS in this population.^{4,10}

Complications

Complications from radiation typically develop 6 to 18 months following treatment and are associated with greater AVM obliteration rates. Approximately 10% of patients develop radiation-induced symptoms, but most are transient and only 1-3% of patients develop permanent neurological changes. Approximately 1-3% of patients can develop cystic changes within the AVM, this usually occurs 6 years following radiation. While most do not cause symptoms, occasionally they can require treatment.^{4,5,10}

Retreatment

If the AVM has not obliterated by 3-5 years, a second radiation treatment is indicated. Retreatment has been shown to be safe and efficacious with obliteration rates following repeat radiation of 35%, 68%, 77%, and 80% at 3, 4, 5, and 10 years, respectively.^{7,9}

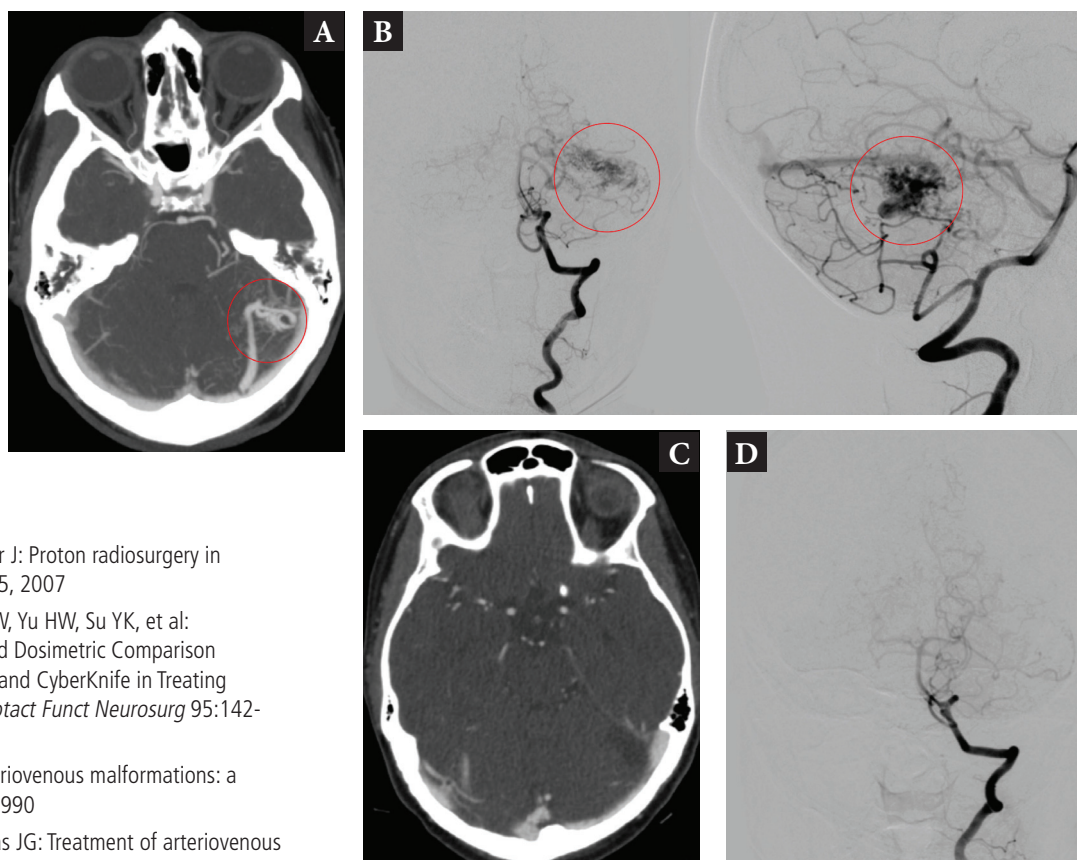
Types of Radiation

Radiosurgical approaches with GK, LINAC, CK, and Proton Beam have similar results. GK has traditionally secured the head for treatment using a frame, with pins that penetrate the bones of the skull and is done using local anesthesia.^{4,10,11}

At the BIDMC Brain Aneurysm Institute, we use the newer technology, the CyberKnife, that tracks the head position and so does not require a frame and a computer-controlled robot delivers the radiation. Radiation treatment is typically completed in 1-3 sessions. Figure two shows our newer device.

Conclusion

Stereotactic radiosurgery has become an established noninvasive treatment modality for intracranial AVMs and is most effective for small AVMs in deep and eloquent locations. Overall, SRS has been shown to achieve high obliteration rates of 70-80% and carry a low complication profile most of which is transient.



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▲ **Figure 1:** Case illustration of a 26-year-old woman with a left cerebellar AVM treated with stereotactic radiosurgery (SRS).

(A) The head CTA before the procedure reveals an AVM measuring 2.25 cm on its maximum diameter. The patient was neurologically intact.

(B) The patient's pre-operative angiography revealed that the main blood supply comes from the left superior cerebellar artery. Venous drainage was from a single large draining vein draining into the torcula.

The patient consented for SRS, which was carried out by radiating the AVM with 2000 cGy in a single fraction. The patient tolerated the procedure and no immediate complications were observed. Short-term follow-up was uneventful.

A 5 years follow-up CTA (C) and angiography (D) demonstrate complete AVM disappearance. The patient remained neurologically intact.



▲ **Figure 2:** Cyberknife device which has recently been upgraded for the most modern treatment of AVMs using stereotactic radiosurgery.



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BIDMC Brain Aneurysm Institute

Opens New Philips 'Azurion system to perform minimally invasive procedures

Beth Israel Deaconess Medical Center (BIDMC) Brain Aneurysm Institute has installed the newest, leading interventional-neuro technology with Philips 'Azurion B20/15 Clarity' system on July 5, 2018. The Azurion is the industry's leading equipment for minimally-invasive neuro interventions with workflow enhancements and 3-Dimensional capabilities to help support the most efficient procedures at the lowest radiation exposure. Clarity IQ image processing enables the surgeons to see even the smallest lesions in great detail without increasing dose to the patients and operators. With the integration of Image Stream Video capabilities, dozens of image sources can be routed anywhere in the interventional lab for optimal flexibility to round off what is truly a state-of-the-art suite. BIDMC is the first institution in the Northeast with this latest platform from Philips, an industry leader in interventional X-Ray.